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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/046,491 | 10/29/2001 | Steven L. Wechsler | 18810-82002 | 6806 |

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| EXAMINER |
|---|
| WEHBE, ANNE MARIE SABRINA |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/046,491 | WECHSLER ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *185-202* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *201* is/are allowed.

6)☒ Claim(s) *185-187,189-191,200 and 202* is/are rejected.

7)☒ Claim(s) *188 and 192* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicant's preliminary amendment filed on 10/29/01 has been entered. As requested, claims 1-184 have been canceled, and new claims 185-202 have been added. Claims 185-202 are currently pending and under examination in the instant application. An action on the merits follows.

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the citizenship of inventor Anthony B. Nesburn.

### *Information Disclosure Statement*

The reference number 35., Huard, J. et al., in the information disclosure statement filed on 10/29/01 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it does not provide a date for this reference. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that

the date of any resubmission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all requirements for statements under 37 CFR 1.97(e). See MPEP § 609 subsection III, C(1).

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 195-200 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims recite mammalian cells which contain an HSV-1 derived vector. Claim 199, which depends on claim 195, recites wherein the cell is contained in a human. Claims which read on cells present in a human encompass the human being. Humans are non-statutory subject matter. It is suggested that applicants amend the claim 195 to recite either a "non-human mammalian cell", or " an isolated mammalian cell", and to amend claim 199 accordingly.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 195-200 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 195, from which claims 196-200 depend, recites a mammalian cell containing an HSV-1 derived vector. Claims 198 recites wherein the cell is contained in a glioma or tumor, and claim 199 recites wherein the cell is contained within a human or other type of mammal. Based on the limitations of claims 198-199, it is unclear whether the applicant intends to claim isolated cells or isolated tumor containing the cells, or whether the applicant intends to claim humans or other types of mammals which comprise these cells or tumors. As such, the claims are confusing and the metes and bounds of the claims cannot be determined.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 185-187, 189, 195-197, 199-200, and 202 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,193,980 B1 (2/27/01), hereafter referred to as Efstathiou et al. in view of U.S. Patent No. 6,340,672 B1 (1/22/02), hereafter referred to as Roizmann et al. The applicant claims an HSV-1 derived vector comprising DNA having at least one functional LAT promoter and further having a deletion in both copies of the HSV-1 LAT gene structural region, and a deletion in both copies of the HSV-1 ICP34.5 gene such that functional RNA transcripts encoding the LAT gene product and the ICP34.5 gene product cannot be detected in a cell hosting the vector, and mammalian cells containing said HSV vector. The applicant further claims said vector wherein the vector further comprises an HSV TK gene, or wherein the LAT promoter is operatively linked to a nucleic acid encoding a selected protein. In addition, the applicant claims said cells which are malignant or non-malignant.

Efstathiou et al. teaches recombinant HSV-1 vectors and viruses in which an heterologous DNA is operatively linked to the LAT promoter, thus introducing a deletion into the LAT region such that normal LAT transcripts are not detected (Efstathiou et al., Figure 5, columns 3-4 and columns 13-14). Efstathiou et al. further teaches that the heterologous DNA can encode a reporter gene such as lacZ or a therapeutic gene such as HSV-TK (Efstathiou et al., columns 5, and 9-10). Efstathiou et al. further teaches transducing cells with the recombinant HSV vectors, including cells of the nervous system or neoplastic cells (Efstathiou et al., column 9-10). In addition, Efstathiou et al. teaches that recombinant HSV vectors and viruses can also be lack functional forms of various HSV regulatory proteins, and can be replication defective and/or attenuated (Efstathiou et al., column 6). Efstathiou et al. also provides motivation for using HSV vectors which utilize the LAT promoter to express a heterologous gene over other types of HSV vectors by teaching that expression of the heterologous gene by the LAT promoter persists throughout the latency period of HSV infection thus resulting in long term gene expression (Efstathiou et al., column 3, and column 4).

Efstathiou et al. differs from the instant invention by failing to specifically teach that the HSV vector further lacks the ICP34.5 gene product due to a deletion in both copies of the ICP34.5 gene. Roizman et al. supplements Efstathiou et al. by teaching that the deletion of both copies of the ICP 34.5 gene in an HSV virus result in an attenuated virus designated R3616 with reduced neurovirulence (Roizman et al., columns 16-17, and Figure 2). Roizman

et al. further provides motivation for using an ICP34.5 -/- HSV by teaching that the R3616 virus ranks among the least pathogenic viruses at the time of filing (Roizman et al., column 17, lines 22-24). Therefore, based on the teachings of Efstathiou et al. that it is preferable that the HSV vectors encoding a heterologous gene operatively linked to the LAT promoter be replication defective and/or attenuated, and the teachings of Roizman et al. that an HSV virus having a deletion in both copies of the ICP 34.5 gene is among the least pathogenic of known HSV viruses, it would have been *prima facie* obvious to the skilled artisan to introduce the heterologous gene into the LAT region of the R3616 virus in order to generate an HSV which has decreased neurovirulence and which is capable of expressing the heterologous protein for extended periods of time. Further, based on high degree of skill in the art of molecular biology at the time of filing and the detailed directions provided by both Roizman et al. and Efstathiou et al. for modifying the genome of the HSV virus, the skilled artisan would have had a reasonable expectation of success in making and using the HSV vector which has a deletion in the LAT region, a heterologous gene operatively linked to the LAT promoter, and a deletion in the ICP 34.5 gene.

Claims 190-191, and 193-194 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,193,980 B1 (2/27/01), hereafter referred to as Efstathiou et al. in view of U.S. Patent No. 6,340,672 B1 (1/22/02), hereafter referred to as Roizmann et al., as applied to claims 185-187, 189, 195-197, 199-200, and 202 above, and further in view of

WO 9804726 (2/5/98), hereafter referred to as Coffin et al.. The applicant claims an HSV-1 derived vector comprising DNA having at least one functional LAT promoter and further having a deletion in both copies of the HSV-1 LAT gene structural region, and a deletion in both copies of the HSV-1 ICP34.5 gene such that functional RNA transcripts encoding the LAT gene product and the ICP34.5 gene product cannot be detected in a cell hosting the vector, wherein the LAT promoter is operatively linked to a cytokine, or specifically interferon-gamma.

As discussed in detail above, Efstathiou et al. in view of Roizman et al. provide the teachings and motivation for making HSV vectors which have a deletion in the LAT region, a heterologous gene operatively linked to the LAT promoter, and a deletion in the ICP 34.5 gene. While Efstathiou et al. does teach that the heterologous gene can be a therapeutic gene, Efstathiou et al. does not specifically teach that the gene can be a cytokine. Coffin et al. supplements the teachings of Efstathiou et al. and Roizman et al. by teaching HSV vectors wherein the LAT promoter can be used to express a variety of cytokines and immune effector molecules including interferon-gamma and tumor necrosis factor (Coffin et al., page 8). Thus, provided the motivation for expressing cytokines using the LAT promoter in an HSV vector as taught by Coffin et al., it would have been *prima facie* obvious to the skilled artisan to utilize a cytokine gene such as interferon-gamma or tumor necrosis factor as the therapeutic gene in the HSV vectors taught by Efstathiou et al. in view of Roizman et al.. Further, based on the detailed instructions of modifying HSV vectors as provided by Efstathiou et al.,

Roizman et al., and Coffin et al., the skilled artisan would have had a reasonable expectation of success in making an HSV-1 derived vector comprising DNA having at least one functional LAT promoter and further having a deletion in both copies of the HSV-1 LAT gene structural region, and a deletion in both copies of the HSV-1 ICP34.5 gene such that functional RNA transcripts encoding the LAT gene product and the ICP34.5 gene product cannot be detected in a cell hosting the vector, wherein the LAT promoter is operatively linked to a cytokine, or specifically interferon-gamma.

Claim 191 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,193,980 B1 (2/27/01), hereafter referred to as Efstathiou et al. in view of U.S. Patent No. 6,340,672 B1 (1/22/02), hereafter referred to as Roizmann et al., as applied to claims 185-187, 189, 195-197, 199-200, and 202 above, and further in view of Ho et al. (1996) Mol. Brain. Res., Vol. 41 (1-2), 200-209. The applicant claims an HSV-1 derived vector comprising DNA having at least one functional LAT promoter and further having a deletion in both copies of the HSV-1 LAT gene structural region, and a deletion in both copies of the HSV-1 ICP34.5 gene such that functional RNA transcripts encoding the LAT gene product and the ICP34.5 gene product cannot be detected in a cell hosting the vector, wherein the LAT promoter is operatively linked to a light emitting protein such as luciferase.

As discussed in detail above, Efstathiou et al. in view of Roizman et al. provide the teachings and motivation for making HSV vectors which have a deletion in the LAT region, a

heterologous gene operatively linked to the LAT promoter, and a deletion in the ICP 34.5 gene. While Efstathiou et al. does teach that the heterologous gene can be a reporter gene, such as lacZ, Efstathiou et al. does not specifically teach that the reporter gene can be luciferase. Ho et al. supplements the teachings of Efstathiou et al. and Roizman et al. by teaching various reporter genes which can be used to test the activity of promoters in HSV vectors. Specifically, Ho et al. teaches that lacZ and luciferase can both be used to test promoter activity in *in vitro* and *in vivo* assays, and provides specific examples for each reporter gene (Ho et al., page 206, Figures 6 and 7). Based on the motivation provided by Ho et al. that luciferase is equally efficient as lacZ as a reporter gene in HSV vectors, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use either lacZ or luciferase as a reporter gene in HSV vectors. Further, based on the high level of skill in molecular biology and the detailed directions for modifying HSV vectors provided by Efstathiou et al., Roizman et al. and Ho et al., the skilled artisan would have had a reasonable expectation of success in replacing the lacZ gene taught by Efstathiou et al. with the luciferase gene taught by Ho et al.

Claims 188, 192, and 201 appear to be free of the prior art of record as the prior art of record does not appear to teach or suggest the Prom ΔLAT Δ34.5 HSV vector with or without GFP.

***Claim Objections***

Claims 188 and 192 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 201 appears to be allowable at this time.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER